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FILE 'CAPLUS' ENTERED AT 11:51:27 ON 05 FEB 2006

=> s treatment
L1 8811672 TREATMENT

=> s l1 and anti-PDGF-DD
L2 1 L1 AND ANTI-PDGF-DD

=> d l2 cbib abs

L2 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
2004:252313 Document No. 140:286157 **Anti-PDGF-DD** antibodies for diagnosis and **treatment** of nephritis and related diseases. Floege, Juergen; Gazit-Bornstein, Gadi; Keyt, Bruce; Larochelle, William J.; Lichenstein, Henri (Abgenix, Inc., USA; Curagen Corporation). PCT Int. Appl. WO 2004024098 A2 20040325, 115 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US29414 20030916. PRIORITY: US 2002-2002/PV411137 20020916.

AB Embodiments of the invention described herein relate to antibodies directed to platelet derived growth factor-DD (PDGF-DD) and uses of such antibodies. The antibodies of the invention find use as diagnostics and as **treatments** for diseases associated with the overprodn. of PDGF-DD. In particular, in accordance with embodiments of the invention, the use of **anti-PDGF-DD** antibodies for the **treatment** of nephritis and related disorders, including diseases caused by mesangial proliferation is provided.

=> s l1 and nephritis
L3 14357 L1 AND NEPHRITIS

=> s l3 and antibod?
L4 3716 L3 AND ANTIBOD?

=> s l4 and PDGF-DD
L5 1 L4 AND PDGF-DD

=> d l5 cbib abs

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
2004:252313 Document No. 140:286157 Anti-**PDGF-DD** **antibodies** for diagnosis and **treatment** of **nephritis** and related diseases. Floege, Juergen; Gazit-Bornstein, Gadi; Keyt, Bruce; Larochelle, William J.; Lichenstein, Henri (Abgenix,

Inc., USA; Curagen Corporation). PCT Int. Appl. WO 2004024098 A2 20040325, 115 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US29414 20030916. PRIORITY: US 2002-2002/PV411137 20020916.

AB Embodiments of the invention described herein relate to **antibodies** directed to platelet derived growth factor-DD (**PDGF-DD**) and uses of such **antibodies.** The **antibodies** of the invention find use as diagnostics and as **treatments** for diseases associated with the overprodn. of **PDGF-DD.** In particular, in accordance with embodiments of the invention, the use of anti-**PDGF-DD antibodies** for the **treatment** of **nephritis** and related disorders, including diseases caused by mesangial proliferation is provided.

=> s anti-PDGF-DD
L6 1 ANTI-PDGF-DD

=> d l6 cbib abs

L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
2004:252313 Document No. 140:286157 **Anti-PDGF-DD** antibodies for diagnosis and treatment of nephritis and related diseases. Floege, Juergen; Gazit-Bornstein, Gadi; Keyt, Bruce; Larochelle, William J.; Lichenstein, Henri (Abgenix, Inc., USA; Curagen Corporation). PCT Int. Appl. WO 2004024098 A2 20040325, 115 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US29414 20030916. PRIORITY: US 2002-2002/PV411137 20020916.

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=> s PDGF-DD
L7 44 PDGF-DD

=> s l7 and nephritis
L8 6 L7 AND NEPHRITIS

=> dup remove l8
PROCESSING COMPLETED FOR L8
L9 2 DUP REMOVE L8 (4 DUPLICATES REMOVED)

=> d l9 1-2 cbib abs

L9 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN

2004:252313 Document No. 140:286157 Anti-**PDGF-DD** antibodies for diagnosis and treatment of **nephritis** and related diseases. Floege, Juergen; Gazit-Bornstein, Gadi; Keyt, Bruce; Larochelle, William J.; Lichenstein, Henri (Abgenix, Inc., USA; Curagen Corporation). PCT Int. Appl. WO 2004024098 A2 20040325, 115 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US29414 20030916. PRIORITY: US 2002-2002/PV411137 20020916.

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L9 ANSWER 2 OF 2 MEDLINE on STN DUPLICATE 1

2003398231. PubMed ID: 12937299. A fully human monoclonal antibody (CR002) identifies PDGF-D as a novel mediator of mesangioproliferative glomerulonephritis. Ostendorf Tammo; van Roeyen Claudia R C; Peterson Jeffrey D; Kunter Uta; Eitner Frank; Hamad Avin J; Chan Gerlinde; Jia Xiao-Chi; Macaluso Jennifer; Gazit-Bornstein Gadi; Keyt Bruce A; Lichenstein Henri S; LaRochelle William J; Floege Jurgen. (Division Nephrology, University of Aachen, Germany.) Journal of the American Society of Nephrology : JASN, (2003 Sep) 14 (9) 2237-47. Journal code: 9013836. ISSN: 1046-6673. Pub. country: United States. Language: English.

AB PDGF-B is of central importance in mesangioproliferative diseases. PDGF-D, a new PDGF isoform, like PDGF-B, signals through the PDGF betabeta-receptor. The present study first determined that PDGF-D is mitogenic for rat mesangial cells and is not inhibited by a PDGF-B antagonist. Low levels of PDGF-D mRNA were detected in normal rat glomeruli. After induction of mesangioproliferative **nephritis** in rats by anti-Thy 1.1 mAb, glomerular PDGF-D mRNA and protein expression increased significantly from days 4 to 9 in comparison with nonnephritic rats. Peak expression of PDGF-D mRNA occurred 2 d later than peak PDGF-B mRNA expression. In addition, PDGF-D serum levels increased significantly in the nephritic animals on day 7. For investigating the functional role of PDGF-D, neutralizing fully human mAb were generated using the XenoMouse technology. Rats with anti-Thy 1.1-induced **nephritis** were treated on days 3 and 5 with different amounts of a fully human **PDGF-DD**-specific neutralizing mAb (CR002), equal amounts of irrelevant control mAb, or PBS by intraperitoneal injection. Specific antagonism of PDGF-D led to a dose-dependent (up to 67%) reduction of glomerular cell proliferation. As judged by double immunostaining for 5-bromo-2'-deoxyuridine and alpha-smooth muscle actin, glomerular mesangial cell proliferation was reduced by up to 57%. Reduction of glomerular cell proliferation in the rats that received CR002 was not associated with reduced glomerular expression of PDGF-B mRNA. PDGF-D antagonism also led to reduced glomerular infiltration of monocytes/macrophages (day 5) and reduced accumulation of fibronectin (day 8). In contrast, no effect was noted in normal rats that received an injection of CR002. These data show that PDGF-D is overexpressed in mesangioproliferative states and can act as an auto-, para-, or even endocrine glomerular cell mitogen, indicating that antagonism of PDGF-D may represent a novel therapeutic approach to mesangioproliferative glomerulonephritides.

=> s l7 and mesangial proliferative nephritis
L10 1 L7 AND MESANGIAL PROLIFERATIVE NEPHRITIS

=> d l10 cbib abs

L10 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
2004:252313 Document No. 140:286157 Anti-**PDGF-DD**
antibodies for diagnosis and treatment of nephritis and related diseases.
Floege, Juergen; Gazit-Bornstein, Gadi; Keyt, Bruce; Larochelle, William
J.; Lichenstein, Henri (Abgenix, Inc., USA; Curagen Corporation). PCT
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CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG,
MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA,
ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR,
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(English). CODEN: PIXXD2. APPLICATION: WO 2003-US29414 20030916.
PRIORITY: US 2002-2002/PV411137 20020916.
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of **PDGF-DD**. In particular, in accordance with
embodiments of the invention, the use of anti-**PDGF-DD**
antibodies for the treatment of nephritis and related disorders, including
diseases caused by mesangial proliferation is provided.

=> s l7 and lupus erythematosus
L11 1 L7 AND LUPUS ERYTHEMATOSUS

=> d l11 cbib abs

L11 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
2004:252313 Document No. 140:286157 Anti-**PDGF-DD**
antibodies for diagnosis and treatment of nephritis and related diseases.
Floege, Juergen; Gazit-Bornstein, Gadi; Keyt, Bruce; Larochelle, William
J.; Lichenstein, Henri (Abgenix, Inc., USA; Curagen Corporation). PCT
Int. Appl. WO 2004024098 A2 20040325, 115 pp. DESIGNATED STATES: W: AE,
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IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG,
MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA,
ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR,
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(English). CODEN: PIXXD2. APPLICATION: WO 2003-US29414 20030916.
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embodiments of the invention, the use of anti-**PDGF-DD**
antibodies for the treatment of nephritis and related disorders, including
diseases caused by mesangial proliferation is provided.

=> dup remove l7
PROCESSING COMPLETED FOR L7
L12 12 DUP REMOVE L7 (32 DUPLICATES REMOVED)

=> d l12 1-12 cbib abs

L12 ANSWER 1 OF 12 MEDLINE on STN DUPLICATE 1
2005336950. PubMed ID: 15988036. Platelet-derived growth factor D is activated by urokinase plasminogen activator in prostate carcinoma cells. Ustach Carolyn V; Kim Hyeong-Reh Choi. (Department of Pathology, Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine, 540 E. Canfield, Detroit, Michigan 48201, USA.) Molecular and cellular biology, (2005 Jul) 25 (14) 6279-88. Journal code: 8109087. ISSN: 0270-7306. Pub. country: United States. Language: English.

AB Platelet-derived growth factor (PDGF) protein family members are potent mitogens and chemoattractants for mesenchymal cells. The classic PDGF ligands A and B are single-domain protein chains which are secreted as active dimers capable of activating their cognate PDGF receptors (PDGFRs). In contrast to PDGFs A and B, PDGF D contains an N-terminal complement subcomponent C1r/C1s, Uegf, and Bmp1 (CUB) domain and a C-terminal PDGF domain. PDGF D must undergo extracellular proteolytic processing, separating the CUB domain from the PDGF domain, before the PDGF domain can stimulate beta-PDGFR-mediated cell signal transduction. Here, we report that prostate carcinoma cells LNCaP and PC3 autoactivate latent full-length PDGF D into its active form under serum-independent conditions and that this autoactivation is inhibited by PAI-1, a urokinase plasminogen activator (uPA)/tissue plasminogen activator (tPA) inhibitor. Interestingly, uPA, but not the closely related protease tPA, is capable of processing recombinant latent **PDGF DD** into the active form. We identify the uPA cleavage site between the CUB and PDGF domains of the full-length PDGF D by mutational analysis and show that PDGF D and uPA colocalize in human prostate carcinoma. This evidence provides a direct link between uPA- and PDGF D-mediated cell signaling, which may contribute to the progression of prostate cancer.

L12 ANSWER 2 OF 12 MEDLINE on STN DUPLICATE 2
2005517893. PubMed ID: 16192649. Peroxide-inducible Ets-1 mediates platelet-derived growth factor receptor-alpha gene transcription in vascular smooth muscle cells. Bonello Michelle R; Bobryshev Yuri V; Khachigian Levon M. (Centre for Vascular Research, Department of Pathology, The University of New South Wales, Sydney, NSW 2052, Australia.) The American journal of pathology, (2005 Oct) 167 (4) 1149-59. Journal code: 0370502. ISSN: 0002-9440. Pub. country: United States. Language: English.

AB Platelet-derived growth factor (PDGF) has been implicated in the pathogenesis of vascular occlusive disorders such as atherosclerosis and restenosis in part due to its regulation of smooth muscle cell phenotype. The molecular mechanisms regulating the expression of PDGF-Ralpha, which binds all known dimeric forms of PDGF except **PDGF-DD**, are poorly understood. Here we demonstrate that the winged helix-turn-helix proto-oncogene Ets-1 controls PDGF-Ralpha transcription and mRNA expression in smooth muscle cells. Mutational analysis, electrophoretic mobility shift assay, and chromatin immunoprecipitation revealed the existence of a reverse Ets binding motif (-45TTCC-42) in the proximal region of the PDGF-Ralpha promoter, which bound both recombinant and endogenous Ets-1. Ets-1-inducible PDGF-Ralpha expression depended on the integrity of both the -45TTCC-42 motif and the -61G10(-52) element, which resides upstream of -45TTCC-42 and mediates Sp1 induction. Hydrogen peroxide (H2O2) at nanomolar concentrations stimulated levels of Ets-1 and increased PDGF-Ralpha transcription and mRNA expression without affecting Sp1 expression. H2O2 activation of the PDGF-Ralpha promoter was abolished by disrupting -45TTCC-42 or -61G10(-52). These studies identify a functional Ets motif in the PDGF-Ralpha promoter that plays a pivotal role in agonist-inducible PDGF-Ralpha transcription.

L12 ANSWER 3 OF 12 MEDLINE on STN DUPLICATE 3
2005445381. PubMed ID: 16039137. Expression patterns of PDGF-A, -B, -C and -D and the PDGF-receptors alpha and beta in activated rat hepatic stellate cells (HSC). Breitkopf Katja; Roeyen Claudia van; Sawitza Iris; Wickert Lucia; Floege Jurgen; Gressner Axel M. (Department of Medicine II, Mol.

Alcohol Research in Gastroenterology, University Hospital Mannheim, University of Heidelberg, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany.. katja.breitkopf@med.ma.uni-heidelberg.de) . Cytokine, (2005 Sep 7) 31 (5) 349-57. Journal code: 9005353. ISSN: 1043-4666. Pub. country: United States. Language: English.

AB The platelet-derived growth factor (PDGF) family, which regulates many physiological and pathophysiological processes has recently been enlarged by two new members, the isoforms PDGF-C and -D. Little is known about the expression levels of these new members in hepatic fibrosis. We therefore investigated by quantitative real time PCR (Taqman) the mRNA expression profiles of all four PDGF isoforms in transdifferentiating primary cultured hepatic stellate cells (HSC), an in vitro model system of hepatic fibrogenesis, either with or without stimulation of the cells with PDGF-BB or TGF-beta1. All four isoforms were expressed in HSC transdifferentiating to myofibroblast-like cells (MFB) albeit with different profiles: while PDGF-A mRNA exhibited minor fluctuations only, PDGF-B was rapidly down-regulated. In contrast, both PDGF-C and -D mRNA were strongly induced: PDGF-C up to 5 fold from day 2 to day 8 and PDGF-D up to 8 fold from day 2 to day 5 of culture. Presence of **PDGF-DD** in activated HSC was confirmed at the protein level by immunocytochemistry. Stimulation of HSC and MFB with PDGF-BB led to down-regulation of the new isoforms, whereas TGF-beta1 upregulated PDGF-A only. We further show that PDGF receptor-beta (PDGFR-beta) mRNA was rapidly upregulated within the first day of culture and was constantly expressed from day 2 on while the expression profile of PDGFR-alpha mRNA was very similar to that of PDGF-A during transdifferentiation. Given the dramatic changes in PDGF-C and -D expression, which may compensate for down-regulation of PDGF-B, we hypothesize that the new PDGF isoforms may fulfil specific functions in hepatic fibrogenesis.

L12 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN

2005:553101 Document No. 143:383913 Expression and activity of platelet-derived growth factor receptor-β in breast carcinoma cells. Stoskus, M.; Ger, M.; Tunaitis, V.; Valius, M. (Department of Developmental Biology, Institute of Biochemistry, Vilnius, Lithuania). Biologija (1), 61-63 (English) 2005. CODEN: BOLOE8. ISSN: 1392-0146. Publisher: Lietuvos Mokslu Akademijos Leidykla.

AB The platelet-derived growth factor (PDGF) receptor-β is a member of the type III receptor tyrosine kinase subfamily. PDGF-BB and **PDGF-DD**, ligands for the PDGF receptor-β, activate the receptor by inducing its dimerization and subsequent autophosphorylation at specific tyrosine residues. Phosphorylation causes upregulation of kinase activity of the PDGF receptor and provides binding sites for various downstream signaling mols. Here we show that breast carcinoma cells obtained from different patients express the PDGF receptor. The PDGF receptor also coimmunoppts. with downstream signaling mols., including phosphatidylinositol 3'-kinase and Ras GTPase activating protein. Our data show that the PDGF receptor-β is activated in breast carcinoma cells and indicate a possible role of the receptor in breast cancerogenesis.

L12 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN

2004:252313 Document No. 140:286157 Anti-**PDGF-DD** antibodies for diagnosis and treatment of nephritis and related diseases. Floege, Juergen; Gazit-Bornstein, Gadi; Keyt, Bruce; Larochelle, William J.; Lichenstein, Henri (Abgenix, Inc., USA; Curagen Corporation). PCT Int. Appl. WO 2004024098 A2 20040325, 115 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US29414 20030916.

PRIORITY: US 2002-2002/PV411137 20020916.

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L12 ANSWER 6 OF 12 MEDLINE on STN DUPLICATE 4

2004190879. PubMed ID: 15087386. Platelet-derived growth factor production by B16 melanoma cells leads to increased pericyte abundance in tumors and an associated increase in tumor growth rate. Furuhashi Masao; Sjoblom Tobias; Abramsson Alexandra; Ellingsen Jens; Micke Patrick; Li Hong; Bergsten-Folestad Erika; Eriksson Ulf; Heuchel Rainer; Betsholtz Christer; Heldin Carl-Henrik; Ostman Arne. (Ludwig Institute for Cancer Research, Uppsala Branch, Uppsala, Sweden.) Cancer research, (2004 Apr 15) 64 (8) 2725-33. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB Platelet-derived growth factor (PDGF) receptor signaling participates in different processes in solid tumors, including autocrine stimulation of tumor cell growth, recruitment of tumor stroma fibroblasts, and stimulation of tumor angiogenesis. In the present study, the B16 mouse melanoma tumor model was used to investigate the functional consequences of paracrine PDGF stimulation of host-derived cells. Production of PDGF-BB or **PDGF-DD** by tumor cells was associated with an increased tumor growth rate. Characterization of tumors revealed an increase in pericyte abundance in tumors derived from B16 cells producing PDGF-BB or **PDGF-DD**. The increased tumor growth rate associated with **PDGF-DD** production was not seen in mice expressing an attenuated PDGF beta-receptor and was thus dependent on host PDGF beta-receptor signaling. The increased pericyte abundance was not associated with an increased tumor vessel density. However, tumor cell apoptosis, but not proliferation, was reduced in tumors displaying PDGF-induced increased pericyte coverage. Our findings thus demonstrate that paracrine PDGF production stimulates pericyte recruitment to tumor vessels and suggest that pericyte abundance influences tumor cell apoptosis and tumor growth.

L12 ANSWER 7 OF 12 MEDLINE on STN DUPLICATE 5

2004105407. PubMed ID: 14996732. A potential oncogenic activity of platelet-derived growth factor d in prostate cancer progression. Ustach Carolyn V; Taube Marcus E; Hurst Newton J Jr; Bhagat Sunita; Bonfil R Daniel; Cher Michael L; Schuger Lucia; Kim Hyeong-Reh Choi. (Department of Pathology, Barbara Ann Karmanos Cancer Institute, Wayne State University, School of Medicine, Detroit, Michigan 48201, USA.) Cancer research, (2004 Mar 1) 64 (5) 1722-9. Journal code: 2984705R. ISSN: 0008-5472. Pub. country: United States. Language: English.

AB The platelet-derived growth factor (PDGF) proteins are potent stimulators of cell proliferation/transformation and play a major role in cell-cell communication. For over two decades, PDGFs were thought to exist as three dimeric polypeptides (the homodimers AA and BB and the heterodimer AB). Recently, however, the PDGF C and D chains were discovered in a BLAST search of the expressed sequence tag databases. The PDGF CC and DD dimers have a unique two-domain structure with an NH(2)-terminal CUB (compliment subcomponents C1r/C1s, Uegf, and Bmp1) domain and a COOH-terminal PDGF/vascular endothelial growth factor domain. Whereas secreted PDGF AA, BB, and AB readily activate their cell surface receptors, it was suggested that extracellular proteolytic removal of the CUB domain is required for the PDGF/vascular endothelial growth factor domain of PDGF CC and DD to activate PDGF receptors. In the present study, we examined the processing of latent PDGF D into its active form and the effects of PDGF D expression on prostate cancer progression. We show that LNCaP cells auto-activate latent **PDGF DD** into the active PDGF domain, which can

induce phosphorylation of the beta-PDGF receptor and stimulates LNCaP cell proliferation in an autocrine manner. Additionally, LNCaP-PDGF D-conditioned medium induces migration of the prostate fibroblast cell line 1532-FTX, indicating LNCaP-processed **PDGF DD** is active in a paracrine manner as well. In a severe combined immunodeficient mouse model, **PDGF DD** expression accelerates early onset of prostate tumor growth and drastically enhances prostate carcinoma cell interaction with surrounding stromal cells. These demonstrate a potential oncogenic activity of **PDGF DD** in the development and/or progression of prostate cancer.

L12 ANSWER 8 OF 12 MEDLINE on STN DUPLICATE 6

2004305326. PubMed ID: 15207811. The PDGF family: four gene products form five dimeric isoforms. Fredriksson Linda; Li Hong; Eriksson Ulf. (Ludwig Institute for Cancer Research, Stockholm Branch, Box 240, S-171 77 Stockholm, Sweden.) Cytokine & growth factor reviews, (2004 Aug) 15 (4) 197-204. Ref: 51. Journal code: 9612306. ISSN: 1359-6101. Pub. country: England: United Kingdom. Language: English.

AB Platelet-derived growth factors (PDGFs) were discovered more than two decades ago. Today the PDGF family of growth factors consists of five different disulphide-linked dimers built up of four different polypeptide chains encoded by four different genes. These isoforms, PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC and **PDGF-DD**, act via two receptor tyrosine kinases, PDGF receptors alpha and beta. The classic PDGFs, PDGF-A and PDGF-B, undergo intracellular activation during transport in the exocytic pathway for subsequent secretion, while the novel PDGFs, PDGF-C and PDGF-D, are secreted as latent factors that require activation by extracellular proteases. The classical PDGF polypeptide chains, PDGF-A and PDGF-B, are well studied and they regulate several physiological and pathophysiological processes, mainly using cells of mesenchymal or neuroectodermal origin as their targets. The discovery of two additional ligands for the two PDGF receptors suggests that PDGF-mediated cellular signaling is more complex than previously thought.

L12 ANSWER 9 OF 12 MEDLINE on STN DUPLICATE 7

2003398231. PubMed ID: 12937299. A fully human monoclonal antibody (CR002) identifies PDGF-D as a novel mediator of mesangioproliferative glomerulonephritis. Ostendorf Tammo; van Roeyen Claudia R C; Peterson Jeffrey D; Kunter Uta; Eitner Frank; Hamad Avin J; Chan Gerlinde; Jia Xiao-Chi; Macaluso Jennifer; Gazit-Bornstein Gadi; Keyt Bruce A; Lichenstein Henri S; LaRochelle William J; Floege Jurgen. (Division Nephrology, University of Aachen, Germany.) Journal of the American Society of Nephrology : JASN, (2003 Sep) 14 (9) 2237-47. Journal code: 9013836. ISSN: 1046-6673. Pub. country: United States. Language: English.

AB PDGF-B is of central importance in mesangioproliferative diseases. PDGF-D, a new PDGF isoform, like PDGF-B, signals through the PDGF betabeta-receptor. The present study first determined that PDGF-D is mitogenic for rat mesangial cells and is not inhibited by a PDGF-B antagonist. Low levels of PDGF-D mRNA were detected in normal rat glomeruli. After induction of mesangioproliferative nephritis in rats by anti-Thy 1.1 mAb, glomerular PDGF-D mRNA and protein expression increased significantly from days 4 to 9 in comparison with nonnephritic rats. Peak expression of PDGF-D mRNA occurred 2 d later than peak PDGF-B mRNA expression. In addition, PDGF-D serum levels increased significantly in the nephritic animals on day 7. For investigating the functional role of PDGF-D, neutralizing fully human mAb were generated using the XenoMouse technology. Rats with anti-Thy 1.1-induced nephritis were treated on days 3 and 5 with different amounts of a fully human **PDGF-DD** -specific neutralizing mAb (CR002), equal amounts of irrelevant control mAb, or PBS by intraperitoneal injection. Specific antagonism of PDGF-D led to a dose-dependent (up to 67%) reduction of glomerular cell proliferation. As judged by double immunostaining for 5-bromo-2'-deoxyuridine and alpha-smooth muscle actin, glomerular mesangial cell proliferation was reduced by up to 57%. Reduction of glomerular cell proliferation in the rats that received CR002 was not

associated with reduced glomerular expression of PDGF-B mRNA. PDGF-D antagonism also led to reduced glomerular infiltration of monocytes/macrophages (day 5) and reduced accumulation of fibronectin (day 8). In contrast, no effect was noted in normal rats that received an injection of CR002. These data show that PDGF-D is overexpressed in mesangioproliferative states and can act as an auto-, para-, or even endocrine glomerular cell mitogen, indicating that antagonism of PDGF-D may represent a novel therapeutic approach to mesangioproliferative glomerulonephritides.

L12 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
2002:102055 Document No. 136:289109 New members of the platelet-derived growth factor family of mitogens. Heldin, Carl-Henrik; Eriksson, Ulf; Oestman, Arne (Biomedical Center, Ludwig Institute for Cancer Research, Uppsala, SE-751 24, Swed.). Archives of Biochemistry and Biophysics, 398(2), 284-290 (English) 2002. CODEN: ABBIA4. ISSN: 0003-9861. Publisher: Academic Press.

AB A review is given on the structural and functional properties of the 2 novel members of the platelet-derived growth factor (PDGF) family, PDGF-C and PDGF-D. The PDGF-CC isoform has similar receptor binding-specificity as PDGF-AA and **PDGF-DD** binds only to PDGF β-receptors which differs from PDGF-BB, which binds both to α- and β-receptors. The different expression patterns of the two new PDGF isoforms during the embryonal development indicates that the different PDGF isoforms may have different functions. The PDGF-CC and **PDGF-DD** isoforms may be involved in the development of various disorders. This idea is supported by the finding that overexpression in the heart leads to heart hypertrophy and fibrosis with a phenotype similar to human heart fibrosis. (c) 2002 Academic Press.

L12 ANSWER 11 OF 12 MEDLINE on STN DUPLICATE 8
2001358164. PubMed ID: 11331881. PDGF-D is a specific, protease-activated ligand for the PDGF beta-receptor. Bergsten E; Uutela M; Li X; Pietras K; Ostman A; Heldin C H; Alitalo K; Eriksson U. (Ludwig Institute for Cancer Research, Stockholm Branch, PO Box 240, S-171 77 Stockholm, Sweden.) Nature cell biology, (2001 May) 3 (5) 512-6. Journal code: 100890575. ISSN: 1465-7392. Pub. country: England: United Kingdom. Language: English.

AB The term 'platelet-derived growth factor' (PDGF) refers to a family of disulphide-bonded dimeric isoforms that are important for growth, survival and function in several types of connective tissue cell. So far, three different PDGF chains have been identified - the classical PDGF-A and PDGF-B and the recently identified PDGF-C. PDGF isoforms (PDGF-AA, AB, BB and CC) exert their cellular effects by differential binding to two receptor tyrosine kinases. The PDGF alpha-receptor (PDGFR-alpha) binds to all three PDGF chains, whereas the beta-receptor (PDGFR-beta) binds only to PDGF-B. Gene-targeting studies using mice have shown that the genes for PDGF-A and PDGF-B, as well as the two PDGFR genes, are essential for normal development. Furthermore, overexpression of PDGFs is linked to different pathological conditions, including malignancies, atherosclerosis and fibroproliferative diseases. Here we have identify and characterize a fourth member of the PDGF family, PDGF-D. PDGF-D has a two-domain structure similar to PDGF-C and is secreted as a disulphide-linked homodimer, **PDGF-DD**. Upon limited proteolysis, **PDGF-DD** is activated and becomes a specific agonistic ligand for PDGFR-beta. **PDGF-DD** is the first known PDGFR-beta-specific ligand, and its unique receptor specificity indicates that it may be important for development and pathophysiology in several organs.

L12 ANSWER 12 OF 12 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
2000:478563 Document No.: PREV200000478563. Signaling lymphocytic activation molecule (SLAM) is differentially expressed in human Th1 and Th2 cells. Hamalainen, Heli [Reprint author]; Meissner, Susanne; Lahesmaa, Riitta. Turku Centre for Biotechnology, FIN-20 521, Turku, Finland. Journal of

Immunological Methods, (28 August, 2000) Vol. 242, No. 1-2, pp. 9-19. print.
CODEN: JIMMBG. ISSN: 0022-1759. Language: English.

AB We have used a real-time quantitative RT-PCR technique (TaqMan, PE Biosystems) to identify genes that are differentially expressed by human polarised CD4+ T cell subsets (Th1 or Th2). The goal was to test the feasibility of the detection method in profiling the expression of a set of marker genes important for Th1 and Th2 differentiation. We demonstrate that in polarised human Th1 cells signaling lymphocytic activation molecule (SLAM), a member of the immunoglobulin superfamily, is expressed at 7-25-fold higher levels than in Th2 cells. Along with SLAM, expression of the IL-12 receptor chain beta2 (IL-12Rbeta2) and the IFN-gamma receptor chain beta (IFN-gammaRbeta) proved to be useful molecular markers indicating the state of T cell polarisation, as previously reported. Treatment with IL-12 increased SLAM mRNA expression in T cells by 3-4-fold, whereas a number of other cytokines including PDGF-BB, IFN-alphaA, IFN-alphaA/D, IFN-beta, IFN-gamma or IL-9 had no effect. Stimulating T cells by co-ligating CD3 and CD28 increased SLAM protein surface expression in both Th1 and Th2 cells. In conclusion, real-time RT-PCR detection was found to be an accurate, sensitive and highly reproducible method for fast profiling of mRNA expression in Th1 and Th2 cell subsets.

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=> s glomerulonephritis
L13      95424 GLOMERULONEPHRITIS

=> s l13 and platelete derived growth factor DD
L14          0 L13 AND PLATELETE DERIVED GROWTH FACTOR DD

=> s l13 and PDGF
L15        887 L13 AND PDGF

=> s l15 and anti-PDGF-DD
L16          1 L15 AND ANTI-PDGF-DD

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L16  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2006 ACS on STN
2004:252313   Document No. 140:286157  Anti-PDGF-DD
     antibodies for diagnosis and treatment of nephritis and related diseases.
     Floege, Juergen; Gazit-Bornstein, Gadi; Keyt, Bruce; Larochelle, William
     J.; Lichenstein, Henri (Abgenix, Inc., USA; Curagen Corporation).  PCT
     Int. Appl. WO 2004024098 A2 20040325, 115 pp.  DESIGNATED STATES: W:  AE,
     AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
     CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,
     IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG,
     MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE,
     SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA,
     ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR,
     GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR.
     (English).  CODEN: PIXXD2.  APPLICATION: WO 2003-US29414 20030916.
     PRIORITY: US 2002-2002/PV411137 20020916.
AB   Embodiments of the invention described herein relate to antibodies
     directed to platelet derived growth factor-DD (PDGF-DD) and uses
     of such antibodies.  The antibodies of the invention find use as
     diagnostics and as treatments for diseases associated with the overprodn. of
     PDGF-DD.  In particular, in accordance with embodiments of the
     invention, the use of anti-PDGF-DD
     antibodies for the treatment of nephritis and related disorders, including
     diseases caused by mesangial proliferation is provided.

=> s l15 and anti-PDGF
L17         30 L15 AND ANTI-PDGF
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=> dup remove l17
PROCESSING COMPLETED FOR L17
L18 12 DUP REMOVE L17 (18 DUPLICATES REMOVED)

=> d l18 1-12 cbib abs

L18 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN
2004:252313 Document No. 140:286157 **Anti-PDGF**-DD antibodies for diagnosis and treatment of nephritis and related diseases. Floege, Juergen; Gazit-Bornstein, Gadi; Keyt, Bruce; Larochelle, William J.; Lichenstein, Henri (Abgenix, Inc., USA; Curagen Corporation). PCT Int. Appl. WO 2004024098 A2 20040325, 115 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US29414 20030916. PRIORITY: US 2002-2002/PV411137 20020916.

AB Embodiments of the invention described herein relate to antibodies directed to platelet derived growth factor-DD (**PDGF**-DD) and uses of such antibodies. The antibodies of the invention find use as diagnostics and as treatments for diseases associated with the overprodn. of **PDGF**-DD. In particular, in accordance with embodiments of the invention, the use of **anti-PDGF**-DD antibodies for the treatment of nephritis and related disorders, including diseases caused by mesangial proliferation is provided.

L18 ANSWER 2 OF 12 MEDLINE on STN DUPLICATE 1
2004101392. PubMed ID: 14673633. New perspectives in treatment of **glomerulonephritis.** Coppo Rosanna; Amore Alessandro. (Nephrology, Dialysis and Transplantation Department, Regina Margherita Children's University Hospital, Torino, Italy.. nefrologia@oirmsantanna.piemonte.it) . Pediatric nephrology (Berlin, Germany), (2004 Mar) 19 (3) 256-65. Electronic Publication: 2003-12-13. Ref: 60. Journal code: 8708728. ISSN: 0931-041X. Pub. country: Germany: Germany, Federal Republic of. Language: English.

AB In chronic **glomerulonephritis** (GN) the development of the tissue damage and progression to fibrosis is related to the individual immune response which brings about excessive inflammation, failure to activate regression and glomerular repair and excessive fibrogenic activity. Therefore, the present standard treatment of GN has two aims, to fight the acute inflammation and to inhibit the progressive renal fibrosis. New avenues in the anti-inflammatory and immunosuppressive treatment of the active phase of glomerular diseases include the use of drugs proven to be of value in organ transplantation (mycophenolate mofetil, rapamycin or anti-immune adhesion and anti-co-stimulatory molecules). Interest has recently focused on anti-inflammatory cytokines (monoclonal antibodies, peptidic antagonists or anti-sense oligonucleotides against TNF-alpha, **anti-PDGF**-beta, anti-TGF-beta and cytokine receptor antagonists) and anti-inflammatory natural cytokines (such as IL4, IL10, IL13 or low doses of TGFbeta). Other drugs may act by depleting B cells (such as anti-CD20 monoclonal antibody) or on several immune pathways, such as thalidomide or anti-cyclooxygenase 2. Several anti-sclerogenic drugs are already used for treatment of the chronic phase of glomerular diseases, such as antagonists of angiotensin II, statins and antioxidants. Other drugs are still experimental, including endothelin receptor antagonists and neutral endopeptidase or vasopeptidase inhibitors and other drugs operating on extracellular matrix accumulation/degradation mechanisms, e.g., pirfenidone. There are extremely interesting developments concerning activators of endogenous anti-inflammatory mechanisms, such as those regulated by peroxisome proliferator activated

receptors. There is a need for successful treatment of chronic GN in childhood. This short review of the most promising new drugs shows there is reason to believe that the next decade will provide exciting new tools for the treatment of these diseases in children.

L18 ANSWER 3 OF 12 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
2003:92117 Document No.: PREV200300092117. Mesangial cell proliferation inhibitors for the treatment of proliferative glomerular disease. Kurogi, Yasuhisa [Reprint Author]. R and D Alliances, Otsuka Pharmaceutical Co., Ltd., 463-10, Kagasuno, Kawauchi-cho, Tokushima, 771-0192, Japan. ykurogi@research.otsuka.co.jp. Medicinal Research Reviews, (January 2003) Vol. 23, No. 1, pp. 15-31. print.
ISSN: 0198-6325 (ISSN print). Language: English.

L18 ANSWER 4 OF 12 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 2
2002152250 EMBASE Transferrin up-regulates chemokine synthesis by human proximal tubular epithelial cells: Implication on mechanism of tubuloglomerular communication in glomerulopathic proteinura. Tang S.; Leung J.C.K.; Tsang A.W.L.; Hui Y.L.; Tak M.C.; Kar N.L.. Prof. N.L. Kar, Department of Medicine, University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong, Hong Kong. knlai@hkucc.hku.hk. Kidney International Vol. 61, No. 5, pp. 1655-1665 2002.
Refs: 47.
ISSN: 0085-2538. CODEN: KDYIA5
Pub. Country: United States. Language: English. Summary Language: English.
ED Entered STN: 20020508
AB Background. The pathogenesis of glomerulosclerosis and tubulointerstitial fibrosis in proteinuric renal disease is obscure. We recently showed that transferrin, a key proteinuric component, mediates proximal tubular epithelial cell (PTEC) C3 synthesis. To further examine whether proteinuric tubular injury may induce glomerular inflammation and to characterize the role of transferrin in activating PTEC, glomerular mesangial cells (MC) were exposed to transferrin-activated PTEC culture supernatant and their proliferative and profibrotic responses analyzed. Methods. Human PTEC and MC were obtained by primary culture. Confluent, transferrin-stimulated PTEC were grown in serum-free medium to produce a "conditioned" medium that was incubated with quiescent MC. The proliferative response of MC was then assessed by thymidine uptake, and the expression of fibrogenic factors measured by reverse transcription-polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA). The chemokine profile in PTEC after transferrin treatment was examined by RT-PCR and ELISA. Results. "Conditioned" supernatant from PTEC, which contained the highest amounts of platelet-derived growth factor (**PDGF**), stimulated MC proliferation compared with serum-free (P = 0.03) or transferrin-containing (P = 0.009) control media. This proliferative response was partially abrogated by treating MC with **anti-PDGF**. MC expression of **PDGF**, but not transforming growth factor-β or intercellular cell adhesion molecule-1, was up-regulated by conditioned PTEC medium. Transferrin up-regulated monocyte chemoattractant peptide-1, interleukin-8, and macrophage migration inhibitory factor expression in a time- and dose-dependent fashion, but had no effect on RANTES expression by PTEC. Conclusions. These results provide experimental evidence suggesting that there is a tubuloglomerular "cross-talk" mechanism in the proteinuric state. PTEC-secreted **PDGF**, which further induces mesangial **PDGF**, could partially account for the mesangial proliferation frequently observed in proteinuric renal disease. Transferrin is one of the culprit nephrotic proteins leading to tubular overexpression of various proinflammatory chemokines, which may explain the interstitial changes observed in proteinuric states.

L18 ANSWER 5 OF 12 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
2002:871683 The Genuine Article (R) Number: 605JJ. IL-10 induces mesangial

cell proliferation via a **PDGF**-dependent mechanism. Robertson T E; Nikolic-Paterson D J; Hurst L A; Atkins R C; Chadban S J (Reprint). Royal Prince Alfred Hosp, Missenden Rd, Camperdown, NSW 2050, Australia (Reprint); Monash Univ, Monash Med Ctr, Dept Nephrol, Clayton, Vic 3168, Australia; Monash Univ, Monash Med Ctr, Dept Med, Clayton, Vic 3168, Australia. CLINICAL AND EXPERIMENTAL IMMUNOLOGY (NOV 2002) Vol. 130, No. 2, pp. 241-244. ISSN: 0009-9104. Publisher: BLACKWELL PUBLISHING LTD, 9600 GARSINGTON RD, OXFORD OX4 2DG, OXON, ENGLAND. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Interleukin-10 (IL-10) is a mesangial cell growth factor in vivo and in vitro . However, the mechanism by which IL-10 exerts its mitogenic activity is not known. The aim of this study was to determine whether IL-10 induces mesangial cell proliferation in a **PDGF**-dependent or independent fashion. A well--characterized rat mesangial cell line (1097) was used in a series of cell proliferation experiments in which cells were serum-starved and then incubated with recombinant IL-10 in the presence or absence of STI 571 (a specific inhibitor of signalling via the **PDGF**-alpha and beta receptors) or a neutralizing **anti-PDGF**-AB antibody. IL-10 induced significant mesangial cell proliferation at 24 and 48 h after cytokine addition. This response was inhibited totally by the addition of STI-571, demonstrating that IL-10 mitogenic activity has an absolute requirement for signalling through the **PDGF** receptor. In further studies, it was found that STI-571 could be added 24 h after IL-10 stimulation and still exert a profound inhibition of IL-10 mitogenic activity. The ability of a neutralizing **anti-PDGF**-AB antibody to inhibit completely IL-10-induced mesangial cell proliferation confirmed that IL-10 acts via induction of an autocrine **PDGF** response rather than the possibility that IL-10 may transactivate the **PDGF** receptor in a **PDGF**-independent fashion. In conclusion, this study has demonstrated that IL-10 induces mesangial cell proliferation via an autocrine **PDGF**-mediated mechanism. Thus, therapies which antagonize **PDGF** signalling will also inhibit any contribution of IL-10 to mesangial proliferation.

L18 ANSWER 6 OF 12 MEDLINE on STN DUPLICATE 3

2001448351. PubMed ID: 11316847. Activated coagulation factor X: a novel mitogenic stimulus for human mesangial cells. Monno R; Grandaliano G; Faccio R; Ranieri E; Martino C; Gesualdo L; Schena F P. (Division of Nephrology, Department of Emergency and Transplantation, University of Bari, Bari, Italy.) Journal of the American Society of Nephrology : JASN, (2001 May) 12 (5) 891-9. Journal code: 9013836. ISSN: 1046-6673. Pub. country: United States. Language: English.

AB Intraglomerular activation of the coagulation cascade is a common feature of mesangioproliferative **glomerulonephritis.** Besides thrombin, very little is known about the cellular effects of other components of the coagulation system. This study investigated the effect of activated factor X (FXa) on cultured human mesangial cells. This serine protease induced a significant and dose-dependent increase in DNA synthesis. In addition to its mitogenic effect, FXa caused a striking upregulation of platelet-derived growth factor (**PDGF**) A and B chain gene expression. Next, the intracellular mitogenic signaling pathways activated by FXa were investigated. FXa induced a rapid spike in cytosolic calcium concentration followed by a sustained plateau. This response was not influenced by the downregulation of thrombin receptors. In addition, FXa stimulated a significant upregulation of different tyrosine-phosphorylated proteins. One of these phosphorylated cellular proteins was represented by the c-jun N-terminal kinase, a member of the mitogen-activated protein kinase family. To evaluate the role of FXa enzymatic activity and of **PDGF** autocrine secretion, FXa-induced DNA synthesis was studied in the presence of leupeptin, a specific serine protease inhibitor, and neutralizing **anti-PDGF** antibody. To investigate the role of tyrosine kinase (TK) activation on FXa mitogenic effect, FXa-stimulated thymidine uptake was evaluated in the presence of genistein and herbimycin A, two powerful and specific TK

inhibitors. FXa-elicited DNA synthesis was also examined after protein kinase C (PKC) downregulation by prolonged incubation with phorbol-12-myristate-13-acetate to study the influence of the phospholipase C-PKC axis. The proliferative effect of FXa required its proteolytic activity, and the activation of TK was only partially dependent on PKC activation while it was **PDGF** independent. Finally, it was shown by reverse transcription-PCR that mesangial cells do not express the signaling splicing variant of the putative FXa receptor, effector protease receptor-1. In conclusion, the present study demonstrated that FXa is a powerful mitogenic factor for human mesangial cells, and it induces its cellular effect not through effector protease receptor-1, but most likely by binding a protease-activated receptor and activating phospholipase C-PKC and TK signaling pathways.

L18 ANSWER 7 OF 12 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1996:889813 The Genuine Article (R) Number: VW787. High glucose concentration induces the overexpression of transforming growth factor-beta through the activation of a platelet-derived growth factor loop in human mesangial cells. DiPaolo S (Reprint); Gesualdo L; Ranieri E; Grandaliano G; Schena F P. UNIV BARI POLICLIN, INST NEPHROL, I-70124 BARI, ITALY. AMERICAN JOURNAL OF PATHOLOGY (DEC 1996) Vol. 149, No. 6, pp. 2095-2106. ISSN: 0002-9440. Publisher: AMER SOC INVESTIGATIVE PATHOLOGY, INC, 428 EAST PRESTON ST, BALTIMORE, MD 21202-3993. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB High glucose concentration has been shown to induce the overexpression of transforming growth factor (TGF)-beta 1 mRNA and protein in different cell types, including murine mesangial cells, thus possibly accounting for the expansion of mesangial extracellular matrix observed in diabetic glomerulopathy. In the present study, we evaluated platelet-derived growth factor (**PDGF**) B-chain and **PDGF** -beta receptor gene expression in human mesangial cells (HMCs) exposed to different concentrations of glucose and then sought a possible relationship between a **PDGF** loop and the modulation of TGF-beta 1 expression. NMC [H-3]thymidine incorporation was upregulated by 30 mmol/L glucose (HG) up to 24 hours, whereas it was significantly inhibited at later time points. Neutralizing antibodies to **PDGF** BE abolished the biphasic response to HG, whereas anti-TGF-beta antibodies reversed only the late inhibitory effect of hyperglycemic medium. HG induced an early and persistent increase of **PDGF** B-chain gene expression, as evaluated by reverse transcriptase polymerase chain reaction, whereas **PDGF**-beta receptor mRNA increased by twofold after 6 hours, thereafter declining at levels 70% lower than in controls after 24 hours. I-125-Labeled **PDGF** BE binding studies in HMCs exposed to HG for 24 hours confirmed the decrease of **PDGF**-beta receptor expression. TGF-beta 1-specific transcripts showed 43 and 78% increases after 24 and 48 hours of incubation in HG, respectively, which was markedly diminished by **anti-PDGF** BE neutralizing antibodies or suramin. We conclude that NG induces an early activation of a **PDGF** loop that, in turn, causes an increase of TGF-beta 1 gene expression, thus modulating both HMC proliferation and mesangial matrix production.

L18 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2006 ACS on STN

1996:47024 Document No. 124:107552 Thrombospondin 1 is expressed by proliferating mesangial cells and is up-regulated by **PDGF** and bFGF in vivo. Hugo, Christian; Pichler, Raimund; Meek, Rick; Gordon, Katherine; Kyriakides, Themis; Floege, Jurgen; Bornstein, Paul; Couser, William G.; Johnson, Richard J. (Department Medicine, University Washington, Seattle, WA, USA). Kidney International, 48(6), 1846-56 (English) 1995. CODEN: KDYIA5. ISSN: 0085-2538. Publisher: Blackwell.

AB Thrombospondin 1 has been shown to be linked to **PDGF**-mediated mesangial cell proliferation and migration in vitro, but little is known regarding its expression or regulation in glomerular disease. Exptl. mesangial proliferative nephritis was induced in rats by injection of

anti-Thy1 antibody. Mesangial cell proliferation was associated with de novo expression of thrombospondin 1 mRNA (detected by Northern blot and in situ hybridization) and protein (by Western blot and immunostaining). Although some thrombospondin 1 was expressed by platelets and macrophages, double labeling showed that most thrombospondin 1 mRNA and protein were expressed by proliferating α-actin-pos. mesangial cells. Thrombospondin 1 expression in anti-Thy1 nephritis was complement-dependent and could be reduced by treatment with **anti-PDGF** or anti-bFGF antibodies. Thrombospondin 1 could also be induced in normal rats by infusion of **PDGF** and in rats which were primed with low dose anti-Thy1 antibody by infusion of **PDGF** or bFGF. Thus, this study demonstrates that proliferating mesangial cells express thrombospondin 1 de novo in disease and that thrombospondin 1 expression in vivo is regulated by **PDGF** and bFGF.

L18 ANSWER 9 OF 12 MEDLINE on STN DUPLICATE 4
96094755. PubMed ID: 7495296. Participation of glomerular endothelial cells in the capillary repair of **glomerulonephritis.**
Iruela-Arispe L; Gordon K; Hugo C; Duijvestijn A M; Claffey K P; Reilly M; Couser W G; Alpers C E; Johnson R J. (Department of Pathology, Harvard Medical School, Boston, Massachusetts, USA.) American journal of pathology, (1995 Dec) 147 (6) 1715-27. Journal code: 0370502. ISSN: 0002-9440. Pub. country: United States. Language: English.

AB In many glomerular diseases severe injury to the mesangium may occur, leading to matrix dissolution and damage to the glomerular capillaries. Although the destruction of glomerular architecture may lead to permanent injury, in some cases spontaneous recovery occurs. The mechanisms that mediate this recovery are unknown. In this study we provide evidence for glomerular capillary repair (angiogenesis) in the adult injured glomerulus. Injection of anti-Thy 1 antibody into rats results in severe mesangiolysis with capillary ballooning, microaneurysm formation, and loss of endothelial cells in addition to mesangial cells. Although mesangial proliferation is a major response to injury, proliferation of endothelial cells also can be documented from days 2 to 14 in association with repair of the capillaries. The endothelial cell proliferation peaks on days 2 and 7, when it is seven- to ninefold greater than normal. Many of the endothelial cells display morphological features of angiogenesis. The initial wave of endothelial cell proliferation can be reduced by 40% with neutralizing anti-basic fibroblast growth factor antibodies ($P < 0.001$). The later glomerular endothelial cell proliferation is associated with upregulated expression of vascular permeability factor/endothelial cell growth factor (VPF/VEGF) and an increase of flk, a VPF/VEGF receptor. Although **PDGF** is expressed in this model, **anti-PDGF** antibody treatment did not affect the endothelial cell proliferative response. In summary, glomerular endothelial cells have an active role in the glomerular response to injury. Glomeruli are capable of healing microaneurysms, and the mechanism involves basic fibroblast growth factor- and VPF/VEGF-mediated endothelial proliferative responses.

L18 ANSWER 10 OF 12 MEDLINE on STN DUPLICATE 5
96047748. PubMed ID: 7565476. Multiple roles for platelet-derived growth factor in renal disease. Floege J; Johnson R J. (Division of Nephrology, Medizinische Hochschule Hannover, Germany.) Mineral and electrolyte metabolism, (1995) 21 (4-5) 271-82. Ref: 108. Journal code: 7802196. ISSN: 0378-0392. Pub. country: Switzerland. Language: English.

AB Platelet-derived growth factor (**PDGF**) is a pleiotropic cytokine, that is synthesized by various resident renal cells and also by infiltrating cells. The best established role for **PDGF** in the kidney is the mediation of glomerular mesangial cell proliferation. There is also evidence to suggest an involvement of **PDGF** in the regulation of renal extracellular matrix turnover, the chemoattraction of mesangial cells and/or other cells to sites of injury, the regulation of glomerular hemodynamics, and lipoprotein uptake in the glomerulus. The first studies investigating the efficacy of **anti-PDGF** therapy in glomerular disorders point to a potentially novel approach to

treat progressive renal disease.

L18 ANSWER 11 OF 12 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN

1993:126329 The Genuine Article (R) Number: KN681. TGF-BETA STIMULATES RAT MESANGIAL CELL-PROLIFERATION IN CULTURE - ROLE OF **PDGF** BETA-RECEPTOR EXPRESSION. HABERSTROH U (Reprint); ZAHNER G; DISSER M; THAISS F; WOLF G; STAHL R A K. UNIV FRANKFURT, DEPT MED, DIV NEPHROL, THEODOR STERN KAI 7, W-6000 FRANKFURT 70, GERMANY. AMERICAN JOURNAL OF PHYSIOLOGY (FEB 1993) Vol. 264, No. 2, Part 2, pp. F199-F205. ISSN: 0002-9513. Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Transforming growth factor (TGF)-beta is known to increase mesangial cell (MC) matrix; however, its possible role on MC proliferation is controversial. We therefore studied the influence of TGF-beta on MC proliferation in culture and evaluated its effect on the platelet-derived growth factor (**PDGF**) B-chain as well as the expression of the **PDGF** beta-receptor. TGF-beta (1 ng/ml) increases MC DNA synthesis by approximately threefold after 48 h of incubation. TGF-beta-induced MC proliferation was also confirmed by cell counts. A neutralizing anti-TGF-beta antibody completely blocked this growth promoting activity. The levels of **PDGF** beta-receptor steady-state mRNA were increased by TGF-beta at 48 h. This was associated with an increase in receptor density per cell as measured by receptor kinetic studies. **PDGF** B-chain mRNA was also increased by TGF-beta at 48 h. A neutralizing **anti-PDGF** B-antibody causes no reduction of TGF-beta-induced DNA synthesis; however, suramin completely inhibited the mitogenic effect of TGF-beta. We conclude that TGF-beta stimulates MC growth in long-term culture, a process in which upregulation of the **PDGF** beta-receptor and enhanced synthesis of **PDGF** B-chain might be involved.

L18 ANSWER 12 OF 12 MEDLINE on STN DUPLICATE 6

92235624. PubMed ID: 1569407. Inhibition of mesangial cell proliferation and matrix expansion in **glomerulonephritis** in the rat by antibody to platelet-derived growth factor. Johnson R J; Raines E W; Floege J; Yoshimura A; Pritzl P; Alpers C; Ross R. (Department of Medicine, University of Washington Medical Center, Seattle 98195.) Journal of experimental medicine, (1992 May 1) 175 (5) 1413-6. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB Platelet-derived growth factor (**PDGF**), a potent mitogen for mesenchymal cells in culture, is expressed in vivo in a variety of inflammatory conditions associated with cell proliferation, including atherosclerosis, wound repair, pulmonary fibrosis, and **glomerulonephritis.** However, it is not known if **PDGF** mediates the fibroproliferative responses that characterize these inflammatory disorders. We administered neutralizing **anti-PDGF** IgG or control IgG to rats with mesangial proliferative nephritis. Inhibition of **PDGF** resulted in a significant reduction in mesangial cell proliferation, and largely prevented the increased deposition of extracellular matrix associated with the disease. This suggests that **PDGF** may have a central role in proliferative glomerular disease.

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L19 1996 (FLOEGE J?/AU OR GAZIT-BORNSTEIN G?/AU OR KEYT B?/AU OR LICHENSTEIN H?/AU OR LAROCHELLE W?/AU)

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L20 16 L19 AND ANTI-PDGF

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L21 4 DUP REMOVE L20 (12 DUPLICATES REMOVED)

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L21 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
2004:252313 Document No. 140:286157 **Anti-PDGF**-DD antibodies for diagnosis and treatment of nephritis and related diseases. **Floege, Juergen; Gazit-Bornstein, Gadi; Keyt, Bruce; Larochelle, William J.; Lichenstein, Henri** (Abgenix, Inc., USA; Curagen Corporation). PCT Int. Appl. WO 2004024098 A2 20040325, 115 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US29414 20030916. PRIORITY: US 2002-2002/PV411137 20020916.

AB Embodiments of the invention described herein relate to antibodies directed to platelet derived growth factor-DD (PDGF-DD) and uses of such antibodies. The antibodies of the invention find use as diagnostics and as treatments for diseases associated with the overprodn. of PDGF-DD. In particular, in accordance with embodiments of the invention, the use of **anti-PDGF**-DD antibodies for the treatment of nephritis and related disorders, including diseases caused by mesangial proliferation is provided.

L21 ANSWER 2 OF 4 MEDLINE on STN DUPLICATE 1
96163244. PubMed ID: 8587244. Thrombospondin 1 is expressed by proliferating mesangial cells and is up-regulated by PDGF and bFGF in vivo. Hugo C; Pichler R; Meek R; Gordon K; Kyriakides T; **Floege J** ; Bornstein P; Couser W G; Johnson R J. (Department of Medicine, University of Washington, Seattle, USA.) Kidney international, (1995 Dec) 48 (6) 1846-56. Journal code: 0323470. ISSN: 0085-2538. Pub. country: United States. Language: English.

AB Thrombospondin 1 has been shown to be linked to PDGF-mediated mesangial cell proliferation and migration in vitro, but little is known regarding its expression or regulation in glomerular disease. Experimental mesangial proliferative nephritis was induced in rats by injection of anti-Thy1 antibody. Mesangial cell proliferation was associated with de novo expression of thrombospondin 1 mRNA (detected by Northern blot and in situ hybridization) and protein (by Western blot and immunostaining). Although some thrombospondin 1 was expressed by platelets and macrophages, double labeling showed that most thrombospondin 1 mRNA and protein were expressed by proliferating alpha-actin-positive mesangial cells. Thrombospondin 1 expression in anti-Thy1 nephritis was complement-dependent and could be reduced by treatment with **anti -PDGF** or anti-bFGF antibodies. Thrombospondin 1 could also be induced in normal rats by infusion of PDGF and in rats which were primed with low dose anti-Thy1 antibody by infusion of PDGF of bFGF. Thus, this study demonstrates that proliferating mesangial cells express thrombospondin 1 de novo in disease and that thrombospondin 1 expression in vivo is regulated by PDGF and bFGF.

L21 ANSWER 3 OF 4 MEDLINE on STN DUPLICATE 2
96047748. PubMed ID: 7565476. Multiple roles for platelet-derived growth factor in renal disease. **Floege J**; Johnson R J. (Division of Nephrology, Medizinische Hochschule Hannover, Germany.) Mineral and electrolyte metabolism, (1995) 21 (4-5) 271-82. Ref: 108. Journal code: 7802196. ISSN: 0378-0392. Pub. country: Switzerland. Language: English.

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L21 ANSWER 4 OF 4 MEDLINE on STN DUPLICATE 3
92235624. PubMed ID: 1569407. Inhibition of mesangial cell proliferation and matrix expansion in glomerulonephritis in the rat by antibody to platelet-derived growth factor. Johnson R J; Raines E W; **Floege J** ; Yoshimura A; Pritzl P; Alpers C; Ross R. (Department of Medicine, University of Washington Medical Center, Seattle 98195.) Journal of experimental medicine, (1992 May 1) 175 (5) 1413-6. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

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